REMARKS

FORMAL MATTERS:

Claims 28-55 are pending after entry of the amendments set forth herein, of which claims 30-31 and 34-49 are presently withdrawn.

Claims 28-29, 32-33, and 50-55 were examined. Claims 28-29, 32-33, and 50-55 were rejected. No claims were allowed.

Claims 28, 33 and 52-55 are amended. Support for theses amendments is found in the claims as originally filed, as well as in the specification at, for example, claim 33: page 108, line 4; claims 52 and 54: page 107 line 20; and claims 43 and 55: page 82; line 9.

The specification has been amended to address the objections raised by the Examiner. The specification has been amended on pages 31 and 32 to remove the browser executable code.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

RESTRICTION REQUIREMENT

Applicants acknowledge that claims 30-31 and 34-49 are withdrawn from consideration as being drawn to non-elected invention. Applicants expressly preserve the right to petition for withdrawal of the restriction requirement.

OBJECTIONS TO THE SPECIFICATION

The specification has been amended to address the objections raised by the Examiner. Withdrawal of this objections is respectfully requested.

OVERVIEW OF THE INVENTION

The present invention is based on the finding that particular polymorphisms on the Y chromosome are indicative of the evolutionary heritage and/or paternal lineage in an individual having a Y chromosome. These particular polymorphic genetic segments, and the primers used to identify the polymorphisms for identification and comparison purposes, correspond to regions of the Y chromosome having clustered polymorphisms that are homopolymeric in regions which exhibit a very low mutation

rate. Because little or no recombination occurs in the regions containing these markers, the accumulation of mutations in these regions is preserved as an intact haplotype. This creates a genetic profile that remains intact across the generations. If men share the same derived allele, then they are identical by descent, not just by state. While a very small amount of recurrent or revertant back mutation has been observed at some markers, these anomalies are easily recognized as such because of the high resolution of the Y tree.

The polymorphisms and methods of the present invention provide a simple way of identifying male siblingship as well as a genetic route to identify male children by so called "genebanking" using DNA or blood, or saliva from a child. Furthermore, the Y chromosome polymorphisms can reveal patterns (estimates) of recent gene flow from one gene pool to another, i.e. admixture. As such, the methods of the present invention make the large amount of information contained in the phylogeny of haplotypes accessible for analysis.

As discussed in greater detail in the specification on pages 18-28, the methods of the invention can be applied to determine which form(s) of a polymorphism are present in tested individuals. The specification provides a discussion of a variety of suitable procedures that may be used in testing individuals, and how the results of the tests should be analyzed (see e.g., specification pages 19-23).

Moreover, the specification on pages 23-29 provides discussions on examples of methods of using the polymorphisms of the invention in wide variety of fields where it is desirable to identify known polymorphisms of a particular individual and/or to determine allelic distribution in a group or population. Such described methods include, linkage analysis for the identification of disease loci, evolutionary studies to determine rates of evolution in a population, identification of polymorphisms useful in forensic identification, identification of mutations associated with a disease or predisposition, and genetic marker development.

With a discussion of the general aspects of the invention, we now turn to the rejections of the claims in the Office Action dated February 25, 2003.

REJECTIONS UNDER §112, ¶2: INDEFINITENESS

Claims 28-29, 32-33 and 50-55 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In view of the amendments to the claims and the remarks made herein, this rejection is respectfully traversed.

The Office Action states that the claims 28-29, 32-33, and 50-55 are "unclear because the specification does not define what is specifically encompassed by haplotype Group II markers M249, M247, and M150" (Office Action, page 4). In particular, the Office Action states the following:

> The issue is that, the ordinary practioner, when reading this specification to practice the method as claimed, is unable to do so because the disclosure is unclear, vague and indefinite. What are, in a structural sense, markers M249, M247 and M150? Are these 3 markers defining mutations of haplotype Group II? If so, why are they excluded from Table 2, and furthermore why isn't M60 seen as being exemplary enough to be included with M249, M247, and M150? Furthermore, are these specific markers found consistently in individuals of a specific geographic region? It is not clear what applicant's table 3 is intended to teach. To which haplotype # do each of M249, M247, and M150 correspond and how many people have tested positive for the presence of these markers? Further, what allele is had by each of those people that do carry one of the markers M249(A or G?), M247(T or C?), and M150(C or T?)? There is no fixed definition in the art for what constitutes M249, M247, and M150 or "the plurality of polymorphisms that is representative of allelic forms of at least one haplotype Group II".

M249, M247, and M150 are polymorphism markers that are described in Table 1 of the specification on pages 43-130. Specifically, M249 is described on page 108, M247 is described on page M247, and M150 is described on page 82. As noted above in the overview of the invention, the polymorphic markers of the present invention "identify specific haplotypes in the male population, these haplotypes being indicative of a specific geographical or ethnic origin" (Specification, page 12,

paragraph 46). Moreover a polymorphism refers "to the occurrence of two or more genetically determined alternative sequences or alleles in a population...polymorphisms refer to sequence differences between a reference form and a selected allele, and encompasses single or multiple nucleotide differences" (Specification, page 13, paragraph 47).

Furthermore, the polymorphic markers useful in the invention encompass polymorphisms associated with a disease state, as well as "silent" polymorphisms associated with a wild-type phenotype or in a non-coding region (Specification, pages 13-14, paragraph 47). However, with respect to the present invention, it is irrelevant whether the polymorphic markers define either of these types of mutations. Rather, it is only relevant that the polymorphism be one associated with males who share the origin associated with haplotype Group II. The specification has provided exemplary polymorphisms that, when present, indicate the male belongs to haplotype Group II.

The selection of polymorphic markers M249, M247, and M150 is by and large a product of the restriction requirement imposed by the Patent Office. As Applicants understood it, Applicants were made to select a total of ten nucleotides for examination, including primers and polymorphisms. Applicants selected a total of 9 sequences (3 polymorphic markers and their corresponding exemplary forward and reverse primers) in order to prosecute the polymorphic markers and their corresponding primers in the same application (See Response to Restriction Requirement and Preliminary Amendment, Filed September 29, 2003, and Response to Communication filed January 22, 2004). The selected polymorphic markers are exemplary of haplotype Group II. The polymorphic marker M60 is not necessarily excluded from the currently pending claims. In fact, the scope of the pending claims covers the use of polymorphic marker M60. For example, claim 28 recites use of a plurality of polymorphisms.

The Examiner asks in the Office Action whether the markers are found consistently in individuals of a specific geographic region, and as to how many people have tested positive for the presence of these markers. However, applicants respectfully submit that a male can be assigned to a haplogroup by detection of any of several different markers. The haplogroups were, in fact, defined by analyzing DNA samples from individuals of known ethinic origin, and identifying the polymorphic markers unique to those individuals. The frequency distribution of the ten groups is based on genotyping of more than 1000 globally diverse samples using a hierarchical top down approach as illustrated in

FIG.1 above the global map. The representative branching and frequency of polymorphic markers in TABLE 1 are also shown in FIG. 1.

Thus, the number of people in a haplogroup having any particular marker is not particularly relevant. Rather, the presence of a particular allelic form of a marker *per se* indicates that an individual derives his ethnic origin at least in part from that haplogroup.

Furthermore, the method does not indicate that the *absence* of an allelic form of a marker is indicative of the ethnic origin of the male, but rather that the ***presence*** of the allelic form of the marker is indicative of the ethnic origin of the male (see, e.g., claim 28).

In addition, the Office Action states that "the specification does not identify whether, e.g., M249 in a particular haplotype is an A or a G, it is completely vague and indefinite what has been invented (as well as not described)." However, Applicants respectfully disagree. Table 1 of the specification on pages 43-129, lists the sequences and the names for the polymorphisms, as well as providing a nucleotide change at specific positions for the polymorphic markers. For example, with respect to polymorphism M249, the Table 1 of the specification on page 108, line 4, provides that the nucleotide at position 313 is "A to G."

However, in the spirit of expediting prosecution and without conceding to the correctness of the rejection, claims 33 and 52-55 have been amended to clarify that the **nucleotide at position 313 of M249 is guanine**, the **nucleotide at position 224 of M247 is cytosine**, and the **nucleotide at position 313 of M150 is thymine**.

Therefore, the Applicants submit that the rejection of claims 28-29, 32-33 and 50-55 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the amendments to the claims and the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

REJECTIONS UNDER §112, ¶1: WRITTEN DESCRIPTION

Claims 28-29, 32-33 and 50-55 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In view of the amendments to the claims and the remarks made herein, this rejection is respectfully traversed.

In particular, the Office Action on pages 6 and 7 states the following:

> First and most importantly, in a sequence search of the application's own sequences SEQ ID NO:735(M249), SEQ ID NO:729(M247), and SEQ ID NO:449(M150), major omissions were discovered. SEQ ID NO: 735 was found to lack both an "A" or a "G" at position 313 as proposed by the specification on page 108 to characterize the marker. SEQ ID NO: 449 also lacked both a "C" or a "T" at position 224 as proposed by the specification on page 82. Lastly, SEQ ID NO: 729 lacked the disclosure of a "C" at position 224. If applicant's invention is the method for determining the ethnic origin of a male by analyzing markers with a specific nucleotide present, none of the nucleotides proposed in the specification to be present are disclosed in the specification as filed. Even if arguendo, the sequence disclosure did disclose the nucleotides whose detection is considered by applicant to be the invention, the structure had by these markers is not taught by the specification i.e., M249(A or G?), M247(T or C?), and M150(C or T?).

The Applicants note that the specification on page 130 provides an IUB code legend for variable nucleotides at the denoted positions of the polymorphic marker sequences listed in Table 1. Therefore the specification does indeed provide the entire sequence information for polymorphic markers M249, M247, and M150. Moreover, Table 1 of the specification on pages 43-129, lists the sequences and the names for the polymorphisms, as well as providing the nucleotide change at specific positions for the polymorphic markers. For example, with respect to polymorphism M249, the Table 1 of the specification on page 108, line 4, provides that the nucleotide at position 313 is "A to G."

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CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-212.

Respectfully submitted,
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Date: 5/21/04

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